Title

Use of gender distribution in routine surveillance data to detect potential transmission of gastrointestinal infections among men who have sex with men in England

Authors

P Mook[1, 2], D Gardiner[1a], S Kanagarajah[1a], M Kerac[1, 3, 4], G Hughes[5], N Field[5, 6], N McCarthy[1, 2, 7], C Rawlings[1], I Simms[5], C Lane[8], P. D. Crook[1b]

(1) Field Epidemiology Service, Public Health England, London, UK

(2) Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK

(3) Department of Population Health, London School of Hygiene and Tropical Medicine, London, UK

(4) Leonard Cheshire Disability & Inclusive Development Centre, Department of Epidemiology & Public Health, University College London, UK

(5) HIV and STI Department, National Infection Service, Public Health England, London, UK

(6) Centre for Molecular Epidemiology and Translational Research, Institute for Global Health, University College London, London, UK

(7) National Institute Health Research (NIHR) Health Protection Research Unit in Gastrointestinal Infections, United Kingdom

(8) Gastrointestinal, Emerging and Zoonotic Infections Department, Public Health England, London, UK

[a] These authors contributed equally

[b] Corresponding author

Paul Crook, Consultant Epidemiologist, Field Epidemiology Service, Skipton House, 80 London Road, London, SE1 6LH, UK. Paul.crook@phe.gov.uk

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Gender distribution of GI pathogens, England

Summary

Detecting gastrointestinal infection transmission among men who have sex with men (MSM) in England is complicated by a lack of routine sexual behavioural data. We investigated whether gender distributions might generate signals for increased transmission of gastrointestinal pathogens among MSM. We examined the percentage male of laboratory confirmed patient-episodes for patients with no known travel history for 10 gastrointestinal infections of public health interest in England between 2003 and 2013, stratified by age and region. An adult male excess was observed for *Shigella* spp. (annual maximum 71% male); most pronounced for those aged 25-49 years and living in London, Brighton and Manchester. An adult male excess was observed every year for *Entamoeba histolytica* (range 59.8-76.1% male), giardia (53.1-57.6%) and campylobacter (52.1-53.5%) and for a minority of years for hepatitis A (max. 69.8%) and typhoidal salmonella (max. 65.7%). This approach generated a signal for excess male episodes for six gastrointestinal pathogens, including a characterised outbreak of shigella among MSM. Stratified analyses by geography and age group were consistent with MSM transmission for shigella. Optimisation and routine application of this technique by public health authorities elsewhere might help identify potential gastrointestinal infection outbreaks due to sexual transmission among MSM, for further investigation.

Introduction

Gastrointestinal (GI) pathogens including shigella [1, 2], campylobacter [3, 4], vero cytotoxin-producing *Escherichia coli* (VTEC) [5], giardia [6, 7], *Salmonella enterica* serotype Typhi [8], cryptosporidium [9, 10], hepatitis A [11-14] and enteric protozoans, including *Entamoeba histolytica* [15], can be spread through sexual contact, most commonly among men who have sex with men (MSM)[16]. Risk of infection is likely influenced by sexual practices, infectivity and HIV status [16, 17].

In England, sexual history is not routinely collected for most cases of laboratory confirmed gastrointestinal infections reported to Public Health England (PHE). In the absence of this information, there is the risk that increases or outbreaks among MSM may go undetected. However, increased transmission of GI infections among MSM might produce a detectable signal in the gender distribution among cases reported in routine surveillance data. Gender ratios have been applied previously to demonstrate that HIV infection was transmitted predominantly between heterosexuals in Africa in the 1980's [18] and as a surrogate marker for MSM activity in Atlanta, USA [6].

A rise in *Shigella flexneri* 3a in England has been described among men without a known history of recent travel from 2009. Follow-up of a sub-set of cases suggested that faecal-oral transmission occurred during sexual contact between MSM, many of whom were HIV positive and reported high numbers of regular and casual partners, chemsex (engaging in sexual activities while under the influence of drugs) and meeting sex partners and locating sex parties through social and sexual networking [19-21]. The increase in shigellosis has coincided with increasing trends in other

sexually transmitted infections among MSM, including lymphogranuloma venereum, which have been associated with similar risk behaviours [22-24].

We investigated a range of GI pathogens over an 11 year period to explore whether the gender distribution would provide signals of potential sexual transmission, including known outbreaks among MSM.

Methods

Study population

The study population was residents of England aged 0-65 years, with a laboratory confirmed diagnosis of one of 10 GI pathogens of public health significance reported to PHE with a specimen date between 1 January 2003 and 31 December 2013, known gender and no known history of recent travel. The GI pathogens included were: campylobacter, cryptosporidium, *Entamoeba histolytica*, *Giardia* spp., hepatitis A, norovirus, typhoidal and non-typhoidal salmonellas, shigella, and vero cytotoxin-producing *Escherichia coli* (VTEC).

Data source

Data were extracted from Labbase, the national laboratory reporting system for England until March 2015, which stored data submitted from laboratories throughout England, Wales, Northern Ireland and the Channel Islands. For some pathogens - including shigella and salmonella - further typing is performed on a subset of samples submitted to national reference laboratories and these results supplement the Labbase data.

Data analysis

Confirmed laboratory diagnoses for the same pathogen in the same person within a 2 week period (26 weeks for salmonella) of the earliest specimen were de-duplicated and considered as one case-episode, as per established standards used to de-duplicate Labbase data. This was performed to reduce double counting individuals with persisting gastrointestinal infection who have multiple samples taken (e.g. for establishing clearance).

Analyses were restricted to cases resident in England, based on either the postcode of the case, general practice or reporting laboratory, in priority order. Cases were included if the date of their earliest specimen for a given episode was received by the reporting laboratory between 01 January 2003 and 31 December 2013.

Cases with any known recent foreign travel were excluded from the study. Cases were excluded if the laboratory report form noted the case having had any travel to a foreign country or listed a travel destination which was outside of the UK prior to symptom onset.

In the primary analysis for each pathogen we examined total and annual percentage male and male-to-female ratios for those aged 16-65 years over the study period. We made an assumption that in the absence of transmission among MSM by sexual contact we would expect 50% of cases to be male, with a 1:1 male-to-female ratio, for each pathogen. Binomial exact confidence intervals were calculated for the percentage male and a positive signal generated if the lower confidence interval was above 50%. We also reviewed data to note where male-to-female ratios rose above

two, as an arbitrary cut-off as being suggestive of MSM transmission. Chi-squared tests for linear trend were applied to assess change in the gender distribution over the study period at the 5% level for each pathogen.

For pathogens with a signal, secondary analyses were undertaken. Comparative annual analyses were also conducted by age group (less than 16 years, 16-24 years, 25-49 years, 50-65 years) and areas with relatively high MSM populations in England (London, Brighton and Manchester [25]); termed high risk areas) versus elsewhere in England (termed low risk areas) to explore whether the percentage male and male-to-female ratio varied with expected differences in the MSM population distribution by age group and region. Further investigation of percentage male and male-to-female ratios were conducted for shigella species and phage-types.

Results

Over the study period, 529315 GI infection cases were reported in those aged 16-65 years (Table 1). Of these, 25192 cases (4.8%) were excluded as they reported a travel history, leaving 504123 cases aged 16-65 included in the study with no or unknown travel history.

The percentage of cases aged 16-65 years excluded as travel related (4.8%) ranged by pathogen from 0.1% for norovirus; (n=18) to 56.9% for typhoidal salmonella (n=1959) (Table 1). The percentage of cases classified as having an unknown travel history (81%, n=428669) ranged from 36.2% (1247) for typhoidal salmonella to

92.2% (n=3358) for hepatitis A. The number of cases included ranged from 1483 for typhoidal salmonella to 382641 for campylobacter.

Over the whole 11 year study period combined, a positive signal (a male percentage with a lower confidence interval higher than 50%) was observed in adults (16-65 years) for six out of the 10 pathogens studied (*Entamoeba histolytica* 68.3% male, hepatitis A 61.1%, typhoidal salmonella 55.4%, giardia 54.8%, campylobacter 52.8%, shigella spp. 51.3%) and in three out of four of the shigella species and phage-types studied (Table 2). The largest number of excess adult male cases was observed for campylobacter (21649) and the highest adult male percentage was observed for *Shigella flexneri* PT3a cases (89.3%). An excess of females was observed among adults for cryptosporidium, norovirus, non-typhoidal salmonella, VTEC and *Shigella sonnei.* For three of the six pathogens with a male excess in adults (*Shigella* spp., campylobacter and giardia), there was a corresponding male excess in children, which was not observed for *Entamoeba histolytica,* typhoidal salmonella, and hepatitis A. For *Shigella* spp. as a whole, a positive signal was seen in high risk areas (62.5% male) but not in low risk areas (44.8%) or in children (52.1%). For *Shigella flexneri,* there was a positive signal for *Shigella flexneri* in adults, in both high (73.7% male) and low risk areas (53.2%), but not in children. For *Shigella sonnei* there was a positive signal in high risk areas (60% male) and in children (52.7%) but not in low risk areas (41.9%).

When reviewing individual years, no positive signals were observed in any of the 11 study years for cryptosporidium, norovirus, non-typhoidal salmonella, or VTEC (Table 3, Figure 1).

A positive signal for *Shigella* spp. in adults first occurred in 2011 with a subsequent significant rise (max. 71%, max m:f ratio 2.5), *Shigella flexneri* from 2010 onwards (max. 84.1%, max m:f ratio 5.3) and *Shigella sonnei* from 2012 (max. 63.5%, max m:f ratio 1.7) (Figures 1 and 2, Tables 3 and 4). A stronger signal in adults was seen for *Shigella flexneri* PT2a (max 84.1%, max m:f ratio 5.3) and *Shigella flexneri* PT3a (max 100%, max m:f ratio ∞). Annual data by age group and location for *Shigella* spp. showed male exceedances being higher, earlier and more frequent in those aged 25-49 years than other age groups, and for cases in high risk areas compared to low risk areas (Supplementary material S1). No individual year male excess was observed for *Shigella* spp. in children.

For *Entamoeba histolytica* a positive signal in adults was observed in all of the 11 study years for all adults (max. 76.1%, max m:f ratio 3.2), in 10 study years for those aged 25-49 years, in three years for those aged 50-65 years, in no years for 16-24 year olds and once for children (Figure 1, Supplementary material S2). A positive signal was observed in nine study years for both high risk and low risk areas.

A positive signal in adults was observed for hepatitis A in six out of 11 study years (max. 69.8%, with a significant falling linear trend at the 5% level) with signals were

more frequently observed in cases aged 25-49 years (six years), than those aged 16-24 years (four) and children (one), and from low risk (seven) compared with high risk areas (four) (Figure 1, Table 3, Supplementary material S3).

For typhoidal salmonella a positive signal in adults was observed in three of the 11 study years (max. 65.7% with a significant falling trend) and signals were more frequently seen in cases aged 25-49 years (three years), than those aged 16-24 years (none), children (one), and in cases from high risk areas (three) than low risk areas (one) (Figure 1, Table 3, Supplementary material S4).

Positive signals were observed in adults for every year of the study period for campylobacter (maximum 53.5%, max m:f ratio 1.1) (Figure 1, Table 3). A signal was observed in nearly every year for each age group and every year for low risk areas and in nine study years in high risk areas. The percentage male was higher in children than in adults.

For giardia, a positive signal in adults was observed for each of the 11 study years (max 57.6%, max m:f ratio 1.4)(Figure 1, Table 3). A signal was more frequently observed for adults aged 25-49 years and children (all years), compared to 16-24 year olds (two years) and 50-65 year olds (one), and in low risk areas (all years) compared to high risk areas (ten).

For adults aged 15-65 years a male-to-female ratio of cases above an arbitrary cut off of two was only observed for *Entamoeba histolytica,* hepatitis A and *Shigella* spp. for England as a whole (Table 3). For hepatitis A and *Entamoeba histolytica* there were no occasions where the male-to-female ratio was above two and where the adult male percentage did not also provide a signal. There was a mixed picture for shigella. For *Shigella flexneri* the male-to-female ratio rose above two in 2012, later than the first adult male percentage signal (2010) (Table 4). For *Shigella flexneri* PT2a and PT3a the male-to-female ratio rose above two prior to the adult male percentage signal (albeit with small numbers of cases). For *Shigella sonnei,* the male-to-female ratio did not rise above two, while the percentage adult male did signal from 2012.

Discussion

We have applied analysis of male percentage and male-to-female ratios to surveillance data to identify excess gastrointestinal infections among males. This approach generated positive signals for excess male episodes for a period with a well-characterised increase in shigella among MSM. Positive signals were also observed for campylobacter, *Entamoeba histolytica,* giardia, typhoidal salmonella and hepatitis A. No signals were detected for cryptosporidium, norovirus, VTEC or non-typhoidal salmonella spp. Our analysis suggests that routinely collected national surveillance data can be used to help assess the potential contribution of sexual exposure to the transmission of GI pathogens and to detect emerging outbreaks in MSM. Male excess analysis should be seen as hypothesis generating and any signal

detected needs further thorough case level investigation to confirm sexual transmission among MSM.

When using male excess signals among adults to highlight potential MSM transmission, other factors that may result in a male excess need to be considered, including an excess of males in the population, a reduction in female cases, changes in testing and reporting practice, gender specific health seeking behaviour, or random variation. Furthermore, other gender disparities in behaviour such as travel, childcare, injecting drug use and food consumption may influence exposure to GI pathogens such that comparison with a 1:1 male-to-female ratio may not be appropriate. However, adult females are more likely to present to primary care than adult males likely resulting in a testing bias that would tend to lower the male-to-female ratio [26]. To strengthen the hypothesis that a signal truly represents an increase in MSM sexual transmission, one would expect the signal to be greater in adult males aged 25-49 years compared to other age groups, especially children. A greater signal in high risk areas may also support the hypothesis for widespread MSM sexual transmission contributing to overall cases.

While we analysed a large national 11 year dataset there were limitations. Recent travel history was poorly reported. Inclusion of cases with undocumented travel history might lead to misclassification of travel associated infection as domestically acquired. The extent and direction of potential bias is difficult to determine and will vary by pathogen, as it is dependent on a number of factors, including the proportion of cases reporting travel abroad, the proportion of missing travel information, the likelihood of sexual transmission while abroad and gender differences in travel

abroad. International Passenger Survey (IPS) data for 2013 indicates that UK adult males are more likely to travel internationally than females [27] and therefore misclassification may lead to an increase in the observed male percentage. However, misclassification may result in dilution of effect if a high proportion of unknown travel history cases are both likely to be travel related and associated with food- or waterborne infection and such exposure is independent of gender. The numbers presented here likely underestimate the true counts as not all cases in the community present to health care or provide specimens (and the proportion who do differ by pathogen) [28].

Use of the male-to-female ratio as a marker for MSM activity has been applied previously and its usefulness described [6, 18]. Retrospective application of our method detected the known increase in *S. flexneri* PT 2a and 3a and *S. sonnei* among MSM [19, 29], and an outbreak of hepatitis A among MSM in 2004 [30]. However, other years in which there was a positive signal for hepatitis A coincided with documented outbreaks among people who inject drugs [31, 32], who are over-represented by young adults and men [33], and the Orthodox Jewish Community [34]. Overall, then, our refined approach using age and geographical strata has validated the use of male-to-female ratio for highlighting potential MSM transmission.

The age and geographical distributions of excess male signals for *Shigella* spp. were consistent with MSM-mediated transmission. Signals were more frequently observed in areas with large MSM populations and high rates of other sexually transmitted infections such as London, Brighton and Manchester, and no signal was seen among children. Application of the excess male percentage method to distinct

species and age groups appeared to provide more discriminatory power. A signal was detected one year earlier both for *Shigella* spp. in adults aged 25-49 years when compared to all adults, and for *Shigella flexneri* when compared to *Shigella* spp.. It is possible that more signals for other organisms would have been observed with further discriminatory typing data.

Among other pathogens with positive signals for male excess cases, *Entamoeba histolytica* and hepatitis A showed the strongest indication of likely MSM transmission, with more signals in adults than in children, and for *Entamoeba histolytica,* stronger signals in high risk compared to low risk areas. Transmission among MSM has been well described for both these organisms [11-13, 15]. The episodic positive signal for typhoidal salmonella may reflect the effect of bias arising from incomplete travel information as the majority of cases included in the study with no unknown travel were likely to have travelled (57% of typhoidal salmonella cases identified were excluded due to known travel and only 7% were known not to have travelled).

The consistent slight male excess of campylobacter and giardia are of interest. The burden of campylobacter in England is much greater than other GI infections and therefore we found a very high total excess number of adult males over the study period. Transmission among MSM have been described for both campylobacter [3, 4] and giardia [6, 7], however, the finding for both organisms that the excess is consistent in individual years, in both children and adults, and in low as well as high risk areas may mean that gender factors other than sexual transmission are important in explaining the male excess among adults in this study. Campylobacter

infections in England and Wales have previously been reported to be more common in men up until 15 years and thereafter more common in women [35], and in a study among English residents of Pakistani origin with campylobacter infection, a higher proportion were males [36].

We analysed both the percentage male (applying confidence intervals) and the male-to-female ratio. The sensitivity of using an arbitrary male-to-female ratio threshold e.g. two, to trigger action is greatly influenced by the number of cases due to other transmission routes for each pathogen. In our study the number of campylobacter cases was much higher than shigella cases and for a given number of cases due to sexual transmission among MSM, the male-to-female ratio would be higher for shigella than campylobacter. In addition, the baseline male-to-female ratio in the absence of sexual transmission appears to differ by pathogen e.g. the cryptosporidium male-to-female ratio consistently remained below one. Given these factors, pathogen specific threshold ratios which trigger action could be refined, modelled on historical data.

In our study we excluded all known travel related cases, prioritising identifying domestic sexual transmission. However, MSM may acquire infections due to sexual activity abroad and this method could be refined for each organism to include travel to destinations where it was considered that sexual transmission may be more likely than other transmission routes e.g. via food or water.

Monitoring gender differences can be seen as a supplementary approach to existing measures. Traditional outbreak detection methods e.g. weekly statistical exceedance

of total counts compared to expected values determined from recent years, may detect outbreaks due to MSM transmission, when subsequent descriptive epidemiology points to an excess of adult males. However, there are a number of reasons why MSM outbreaks may be more likely to go undetected than food-borne outbreaks. The person to person nature of MSM transmission (as opposed to point source food-borne outbreaks) may result in a rising tide of cases over many months and therefore may be less to likely trigger weekly exceedances. Furthermore, food-borne outbreaks may be detected due to sick diners recognising a common event and approaching authorities. In contrast, MSM may incorrectly ascribe their illness due to food poisoning and therefore it is less likely that links to sexual transmission events will be reported. A foodborne outbreak may also result in subsequent MSM transmission and so periodic review of gender difference for known prolonged outbreaks may help identify a change in transmission route.

There is growing evidence that transmission of GI pathogens among MSM is becoming a public health concern globally, especially among HIV-positive MSM reporting high risk sexual and drug use behaviours [16, 17, 37-39]. In England, outbreaks of *Shigella flexneri*, have been associated with high rates of hospitalisation and reports of bacteraemia [20, 21]. More recently, there has been an increase in the male-to-female ratio of *Shigella sonnei* cases [29], characterised clusters of extended spectrum beta-lactamase producing *Shigella sonnei* [40], vero cytotoxin-producing *Escherichia coli* O117:H7 among (mostly HIV-positive) MSM [5] and an international outbreak of hepatitis A [14]. Simple methods to improve detection of outbreaks of GI pathogens that may lead to severe health outcomes are therefore needed. In the absence of routinely collected information on sexual orientation,

routine application of this rapid method, refined to use pathogen specific male-to-female ratio or percentage male thresholds at the most granular typing discrimination available, might be a useful tool to alert public health authorities to potential GI infection outbreaks associated with sexual contact among MSM and afford earlier health promotion and interventions. We recommend that this approach be used by other countries to detect excess male cases and prompt further investigations to assess whether sexual transmission of GI pathogens among MSM warrants public health action. Surveillance could be further improved by introducing simple questions on recent sexual exposure in routine questionnaires for GI pathogens.

Acknowledgements

The research was in part funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Gastrointestinal Infections at University of Liverpool in partnership with Public Health England (PHE), in collaboration with University of East Anglia, University of Oxford and the Institute of Food Research. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.

Funding

This work was supported by the National Institute for Health Research (HPRU-2013-10038).

Conflicts of interest

None

References

1. Morgan O, et al. Shigella sonnei outbreak among homosexual men, London. Emerging Infectious Diseases. 2006;12:1458-1460. doi: 10.3201/eid1209.060282.

2. Centers for Disease Control and Prevention. Shigella flexneri serotype 3 infections among men who have sex with men--Chicago, Illinois, 2003-2004. MMWR Morbidity and Mortality Weekly Report. CDC Surveillance Summaries. 2005;54:820-822.

3. Gaudreau C, et al. Campylobacter coli outbreak in men who have sex with men, Quebec, Canada, 2010-2011. Emerging Infectious Diseases. 2013;19:764-767. doi: 10.3201/eid1905.121344.

4. Gaudreau C, Michaud S. Cluster of erythromycin- and ciprofloxacin-resistant Campylobacter jejuni subsp. jejuni from 1999 to 2001 in men who have sex with men, Quebec, Canada. Clinical Infectious Diseases. 2003;37:131-136. doi: 10.1086/375221.

5. Simms I, et al. Identification of verocytotoxin-producing Escherichia coli O117:H7 in men who have sex with men, England, November 2013 to August 2014. Eurosurveillance. 2014;19.

6. Beltrami JF, Shouse RL, Blake PA. Trends in infectious diseases and the male to female ratio: possible clues to changes in behavior among men who have sex with men. AIDS Education and Prevention. 2005;17:49-59. doi: 10.1521/aeap.2005.17.Supplement B.49.

7. Di Benedetto MA, et al. Prevalence of sexually transmitted infections and enteric protozoa among homosexual men in western Sicily (south Italy). Journal of Preventive Medicine and Hygiene. 2012;53:181-185.

8. Reller ME, et al. Sexual transmission of typhoid fever: a multistate outbreak among men who have sex with men. Clinical Infectious Diseases. 2003;37:141-144. doi: 10.1086/375590.

9. Danila RN, et al. Two concurrent enteric disease outbreaks among men who have sex with men, Minneapolis-St Paul area. Clinical Infectious Diseases. 2014;59:987-989. doi: 10.1093/cid/ciu478.

10. Hellard M, et al. Risk factors leading to Cryptosporidium infection in men who have sex with men. Sexually Transmitted Infections. 2003;79:412-414.

11. Bell A, et al. An outbreak of hepatitis A among young men associated with having sex in public venues. Communicable Disease and Public Health. 2001;4:163-170.

12. Bordi L, et al. Monophyletic outbreak of Hepatitis A involving HIV-infected men who have sex with men, Rome, Italy 2008-2009. Journal of Clinical Virology. 2012;54:26-29. doi: 10.1016/j.jcv.2012.01.009.

13. Mazick A, et al. Hepatitis A outbreak among MSM linked to casual sex and gay saunas in Copenhagen, Denmark. Eurosurveillance. 2005;10:111-114.

14. European Centre for Disease Prevention and Control (ECDC). Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men. Stockholm: 2016.

15. Hung CC, Chang SY, Ji DD. Entamoeba histolytica infection in men who have sex with men. Lancet Infectious Diseases. 2012;12:729-736. doi: 10.1016/S1473-3099(12)70147-0.

16. Mitchell H, Hughes G. Recent epidemiology of sexually transmissible enteric infections in men who have sex with men. Current Opinion in Infectious Diseases. 2018;31:50-56. doi: 10.1097/QCO.0000000000000423.

17. Lo YC, Ji DD, Hung CC. Prevalent and incident HIV diagnoses among Entamoeba histolytica-infected adult males: a changing epidemiology associated with sexual transmission--Taiwan, 2006-2013. PLoS Neglected Tropical Diseases. 2014;8:e3222. doi: 10.1371/journal.pntd.0003222.

18. Quinn TC, et al. AIDS in Africa: an epidemiologic paradigm. Science. 1986;234:955-963.

19. Borg ML, et al. Ongoing outbreak of Shigella flexneri serotype 3a in men who have sex with men in England and Wales, data from 2009-2011. Eurosurveillance. 2012;17.

20. Gilbart VL, et al. Sex, drugs and smart phone applications: findings from semistructured interviews with men who have sex with men diagnosed with Shigella flexneri 3a in England and Wales. Sexually Transmitted Infections. 2015;91:598-602. doi: 10.1136/sextrans-2015-052014.

21. Cresswell FV, et al. Shigella flexneri: A cause of significant morbidity and associated with sexually transmitted infections in men who have sex with men. Sexually Transmitted Diseases. 2015;42:344. doi: 10.1097/OLQ.0000000000000295.

22. Childs T, et al. Rapid increase in lymphogranuloma venereum in men who have sex with men, United Kingdom, 2003 to September 2015. Eurosurveillance. 2015;20:30076. doi: 10.2807/1560-7917.ES.2015.20.48.30076.

23. Hughes G, et al. Lymphogranuloma venereum diagnoses among men who have sex with men in the U.K.: interpreting a cross-sectional study using an epidemic

phase-specific framework. Sexually Transmitted Infections. 2013;89:542-547. doi: 10.1136/sextrans-2013-051051.

24. Mohammed H, et al. Increase in sexually transmitted infections among men who have sex with men, England, 2014. Emerging Infectious Diseases. 2016;22:88-91. doi: 10.3201/eid2201.151331.

25. van Kampen S, et al. Producing modelled estimates of the size of the lesbian, gay and bisexual (LGB) population of England. 2017.

26. Briscoe ME. Why do people go to the doctor? Sex differences in the correlates of GP consultation. Social Science and Medicine. 1987;25:507-513.

27. Office for National Statistics International Passenger Survey Travelpac 2013 database (https://www.ons.gov.uk/peoplepopulationandcommunity/leisureandtourism/datasets/travelpac). Accessed 01 February 2018

28. Tam CC, et al. Longitudinal study of infectious intestinal disease in the UK (IID2 study): incidence in the community and presenting to general practice. Gut. 2012;61:69-77. doi: 10.1136/gut.2011.238386.

29. Simms I, et al. Intensified shigellosis epidemic associated with sexual transmission in men who have sex with men--Shigella flexneri and S. sonnei in England, 2004 to end of February 2015. Eurosurveillance. 2015;20.

30. O'Sullivan D. Hepatitis A outbreak in men who have sex with men, London, August-September 2004. Eurosurveillance. 2004;8. doi: https://doi.org/10.2807/esw.08.40.02558-en.

31. Sundkvist T, et al. Outbreak of hepatitis A infection among intravenous drug users in Suffolk and suspected risk factors. Communicable Disease and Public Health. 2003;6:101-105.

32. Syed NA, et al. Outbreak of hepatitis A in the injecting drug user and homeless populations in Bristol: control by a targeted vaccination programme and possible parenteral transmission. European Journal of Gastroenterology and Hepatology. 2003;15:901-906.

33. Hay G, et al. Capture--recapture and anchored prevalence estimation of injecting drug users in England: national and regional estimates. Statistical Methods in Medical Research. 2009;18:323-339. doi: 10.1177/0962280208094687.

34. Edelstein M, et al. Hepatitis A outbreak in an Orthodox Jewish community in London, July 2010. Eurosurveillance. 2010;15.

35. Gillespie IA, et al. Demographic determinants for Campylobacter infection in England and Wales: implications for future epidemiological studies. Epidemiology and Infection. 2008;136:1717-1725. doi: 10.1017/S0950268808000319.

36. Campylobacter sentinel surveillance scheme collaborators. Ethnicity and Campylobacter infection: a population-based questionnaire survey. Journal of Infection. 2003;47:210-216.

37. Wilmer A, et al. Shigella flexneri serotype 1 infections in men who have sex with men in Vancouver, Canada. HIV Medicine. 2015;16:168-175. doi: 10.1111/hiv.12191.

38. Chiou CS, et al. The worldwide spread of ciprofloxacin-resistant Shigella sonnei among HIV-infected men who have sex with men, Taiwan. Clinical Microbiology and Infection. 2016;22:383 e311-383 e316. doi: 10.1016/j.cmi.2015.12.021.

39. Baker KS, et al. Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: a cross-sectional study. Lancet Infectious Diseases. 2015;15:913-921. doi: 10.1016/S1473-3099(15)00002-X.

40. Mook P, et al. ESBL-Producing and macrolide-resistant Shigella sonnei infections among men who have sex with men, England, 2015. Emerging Infectious Diseases. 2016;22:1948-1952. doi: 10.3201/eid2211.160653.

Table 1. Laboratory confirmed gastrointestinal infection cases aged 16-65 years by recent travel status for pathogens, England, 2003-2013

Organism	**Known travel related (%)**	**Known not travel related (%)**	**Unknown (%)**	***Total known not travel related or unknown (%)***	**Total**
Campylobacter spp.	658 (0.2)	50,506 (13.2)	332,135 (86.7)	*382,641 (99.8)*	383,299
Cryptosporidium spp.	470 (2.6)	2,573 (14)	15,334 (83.4)	*17,907 (97.4)*	18,377
Entamoeba histolytica	333 (17.4)	126 (6.6)	1,455 (76)	*1,581 (82.6)*	1,914
Giardia spp.	1,473 (5.6)	3,389 (12.9)	21,387 (81.5)	*24,776 (94.4)*	26,249
Hepatitis A	78 (2.1)	206 (5.7)	3,358 (92.2)	*3,564 (97.9)*	3,642
Norovirus	18 (0.1)	1,290 (10.2)	11,348 (89.7)	*12,638 (99.9)*	12,656
Salmonella spp. (non-typhoidal)	17,794 (27.9)	14,871 (23.3)	31,039 (48.7)	*45,910 (72.1)*	63,704
Salmonella spp (typhoidal)	1,959 (56.9)	236 (6.9)	1,247 (36.2)	*1,483 (43.1)*	3,442
Shigella spp.	1,709 (14)	1,498 (12.3)	9,008 (73.7)	*10,506 (86)*	12,215
Shigella flexneri	*450 (14)*	*462 (14.4)*	*2,291 (71.5)*	*2753 (86)*	*3,203*
Shigella sonnei	*1,047 (14.5)*	*844 (11.7)*	*5,327 (73.8)*	*6,171 (85.5)*	*7,218*
Shigella flexneri PT2a	*88 (27.3)*	*63 (19.6)*	*171 (53.1)*	*234 (72.7)*	*322*
Shigella flexneri PT3a	*66 (16.3)*	*116 (28.7)*	*222 (55)*	*338 (83.7)*	*404*
VTEC	700 (18.3)	759 (19.9)	2,358 (61.8)	*3,117 (81.7)*	3,817
Total	25,192 (4.8)	75,454 (14.3)	428,669 (81.0)	*504,123 (95.2)*	529,315

Table 2. Excess number of male cases, male-to-female ratio and percentage male by pathogen, risk area and age group, for laboratory confirmed gastrointestinal infections with no reported travel history, England, 2003-2013.

Organism	Total cases 16-65 yrs	No. excess males 16-65 yrs	Male-to-female ratio in 16-65 yrs	% Male			
				16-65 yrs all areas	16-65 yrs in high risk areas	16-65 yrs in low risk areas	< 16 yrs
Campylobacter spp.	382,641	21,649	1.12	52.8 (52.7-53.0)	52.1 (51.6-52.6)	52.9 (52.8-53.1)	60.3 (60.0-60.7)
Cryptosporidium spp.	17,907	-4,643	0.59	37.0 (36.3-37.7)	45.8 (43.1-48.6)	36.4 (35.6-37.1)	56.5 (55.9-57.2)
Entamoeba histolytica	1,581	579	2.16	68.3 (65.9-70.6)	74.4 (70.9-77.6)	63.5 (60.3-66.7)	58.4 (48.8-67.6)
Giardia spp.	24,776	2,396	1.21	54.8 (54.2-55.5)	58.5 (56.9-60.1)	54.2 (53.5-54.9)	58.2 (56.9-59.4)
Hepatitis A	3,564	792	1.57	61.1 (59.5-62.7)	54.0 (51.0-57.1)	64.0 (62.1-65.9)	51.8 (48.3-55.2)
Norovirus	12,638	-858	0.87	46.6 (45.7-47.5)	52.5 (49.0-56.0)	46.2 (45.3-47.1)	56.0 (54.9-57.2)
Salmonella spp. (non-typhoidal)	45,910	-816	0.97	49.1 (48.7-49.6)	48.8 (47.8-49.8)	49.2 (48.7-49.7)	53.1 (52.5-53.8)
Salmonella spp. (typhoidal)	1,483	161	1.24	55.4 (52.9-58.0)	56.4 (52.8-59.9)	54.4 (50.6-58.1)	53.6 (48.9-58.3)
Shigella spp.	10,506	272	1.05	51.3 (50.3-52.3)	62.5 (60.9-64.0)	44.8 (43.6-46.0)	52.1 (50.2-54.0)
S. flexneri	2753	651	1.62	61.8 (60.0-63.6)	73.7 (71.1-76.3)	53.2 (50.7-55.7)	50.2 (46.8-53.6)
S. sonnei	6,171	-261	0.92	47.9 (46.6-49.1)	60.0 (57.9-62.2)	41.9 (40.4-43.5)	52.7 (50.1-55.3)
S. flexneri PT2a	234	102	2.55	71.8 (65.6-77.5)	86.4 (78.5-92.2)	58.9 (49.7-67.6)	44.0 (33.2-55.3)
S. flexneri PT3a	338	266	8.39	89.3 (85.6-92.4)	99.0 (96.3-99.9)	85.9 (78.7-91.4)	34.2 (19.6-51.4)
VTEC	3,117	-673	0.64	39.2 (37.5-40.9)	35.5 (30.0-41.3)	39.6 (37.8-41.4)	51.4 (49.8-53.1)
Total	504,123	18,859					

Ratios above a threshold of two or where the percentage male has a lower confidence interval above 50% are shaded.

Table 3. Cases aged 16 to 65 years diagnosed with certain gastrointestinal infections with no reported travel history, by sex, male-to-female ratio and percentage male, England, 2003-2013 (n=504,123)

Organism	Sex, m:f ratio and percentage male	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p value[†]
Campylobacter spp.	Female	14,559	13,981	14,986	14,451	15,713	14,929	17,552	18,977	19,295	18,934	17,119	**180,496**	0.114
	Male	16,250	15,910	16,386	16,287	17,587	16,720	19,127	21,067	21,572	21,509	19,730	**202,145**	
	Ratio	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.2	**1.1**	
	Percentage (95% CI)	52.7 (52.2-53.3)	53.2 (52.7-53.8)	52.2 (51.7-52.8)	53.0 (52.4-53.5)	52.8 (52.3-53.4)	52.8 (52.3-53.4)	52.1 (51.6-52.7)	52.6 (52.1-53.1)	52.8 (52.3-53.3)	53.2 (52.7-53.7)	53.5 (53.0-54.1)	**52.8 (52.7-53)**	
Cryptosporidium spp.	Female	1,109	793	957	921	812	1,041	1,211	1,011	721	1,690	1,009	**11,275**	0.259
	Male	674	539	532	565	471	600	627	585	462	979	598	**6,632**	
	Ratio	0.6	0.7	0.6	0.6	0.6	0.6	0.5	0.6	0.6	0.6	0.6	**0.6**	
	Percentage (95% CI)	37.8 (35.5-40.1)	40.5 (37.8-43.2)	35.7 (33.3-38.2)	38.0 (35.5-40.5)	36.7 (34.1-39.4)	36.6 (34.2-38.9)	34.1 (31.9-36.3)	36.7 (34.3-39.1)	39.1 (36.3-41.9)	36.7 (34.8-38.5)	37.2 (34.8-39.6)	**37.0 (36.3-37.7)**	
Entamoeba histolytica	Female	56	71	61	48	33	51	29	30	34	56	32	**501**	0.365
	Male	134	150	135	110	77	76	70	53	108	104	63	**1,080**	
	Ratio	2.4	2.1	2.2	2.3	2.3	1.5	2.4	1.8	3.2	1.9	2.0*	**2.2**	
	Percentage (95% CI)	70.5 (63.5-76.9)	67.9 (61.3-74)	68.9 (61.9-75.3)	69.6 (61.8-76.7)	70 (60.5-78.4)	59.8 (50.8-68.4)	70.7 (60.7-79.4)	63.9 (52.6-74.1)	76.1 (68.2-82.8)	65 (57.1-72.4)	66.3 (55.9-75.7)	**68.3 (66-70.6)**	
Giardia spp.	Female	923	899	876	875	905	1039	1080	1163	1144	1180	1106	**11,190**	<0.001
	Male	1250	1219	1097	1058	1102	1226	1227	1317	1390	1418	1282	**13,586**	
	Ratio	1.4	1.4	1.3	1.2	1.2	1.2	1.1	1.1	1.2	1.2	1.2	**1.2**	
	Percentage (95% CI)	57.5 (55.4-59.6)	57.6 (55.4-59.7)	55.6 (53.4-57.8)	54.7 (52.5-57)	54.9 (52.7-57.1)	54.1 (52-56.2)	53.2 (51.1-55.2)	53.1 (51.1-55.1)	54.9 (52.9-56.8)	54.6 (52.6-56.5)	53.7 (51.7-55.7)	**54.8 (54.2-55.5)**	
Hepatitis A	Female	244	135	98	84	159	260	140	65	52	66	83	**1,386**	<0.001
	Male	537	283	227	159	159	285	151	141	82	88	66	**2,178**	
	Ratio	2.2	2.1	2.3	1.9	1.0	1.1	1.1	2.2	1.6	1.3	0.8	**1.6**	
	Percentage (95% CI)	68.8 (65.4-72)	67.7 (63-72.2)	69.8 (64.5-74.8)	65.4 (59.1-71.4)	50.0 (44.4-55.6)	52.3 (48-56.6)	51.9 (46-57.8)	68.4 (61.6-74.7)	61.2 (52.4-69.5)	57.1 (48.9-65.1)	44.3 (36.2-52.7)	**61.1 (59.5-62.7)**	
Norovirus	Female	237	343	289	411	577	652	802	1,077	761	919	680	**6,748**	0.001
	Male	195	259	217	355	461	526	670	980	683	920	624	**5,890**	

	Ratio	0.8	0.8	0.8	0.9	0.8	0.8	0.8	0.9	0.9	1.0	0.9	**0.9**	
	Percentage (95% CI)	45.1 (40.4-50)	43.0 (39.0-47.1)	42.9 (38.5-47.3)	46.3 (42.8-49.9)	44.4 (41.4-47.5)	44.7 (41.8-47.5)	45.5 (42.9-48.1)	47.6 (45.5-49.8)	47.3 (44.7-49.9)	50.0 (47.7-52.3)	47.9 (45.1-50.6)	**46.6 (45.7-47.5)**	
Salmonella spp. (non-typhoidal)	Female	3,393	3,092	2,446	2,770	2,610	1,824	1,703	1,407	1,489	1,380	1,249	**23,363**	0.032
	Male	3,213	3,197	2,434	2,648	2,467	1,732	1,763	1,335	1,335	1,244	1,179	**22,547**	
	Ratio	0.9	1.0	1.0	1.0	0.9	0.9	1.0	0.9	0.9	0.9	0.9	**1.0**	
	Percentage (95% CI)	48.6 (47.4-49.9)	50.8 (49.6-52.1)	49.9 (48.5-51.3)	48.9 (47.5-50.2)	48.6 (47.2-50.0)	48.7 (47.1-50.4)	50.9 (49.2-52.5)	48.7 (46.8-50.6)	47.3 (45.4-49.1)	47.4 (45.5-49.3)	48.6 (46.6-50.6)	**49.1 (48.7-49.6)**	
Salmonella spp. (typhoidal)	Female	36	54	54	68	73	83	71	60	72	44	46	**661**	0.038
	Male	69	55	76	100	84	100	87	91	74	41	45	**822**	
	Ratio	1.9	1.0	1.4	1.5	1.2	1.2	1.2	1.5	1.0	0.9	1.0	**1.2**	
	Percentage (95% CI)	65.7 (55.8-74.7)	50.5 (40.7-60.2)	58.5 (49.5-67.0)	59.5 (51.7-67.0)	53.5 (45.4-61.5)	54.6 (47.1-62.0)	55.1 (47.0-63)	60.3 (52.0-68.1)	50.7 (42.3-59.0)	48.2 (37.3-59.3)	49.5 (38.8-60.1)	**55.4 (52.9-58.0)**	
Shigella spp.	Female	342	410	510	447	608	527	612	611	434	314	302	**5117**	<0.001
	Male	273	413	400	319	450	457	465	649	582	640	741	**5389**	
	Ratio	0.8	1.0	0.8	0.7	0.7	0.9	0.8	1.1	1.3	2.0	2.5	**1.1**	
	Percentage (95% CI)	44.4 (40.4-48.4)	50.2 (46.7-53.7)	44 (40.7-47.3)	41.6 (38.1-45.2)	42.5 (39.5-45.6)	46.4 (43.3-49.6)	43.2 (40.2-46.2)	51.5 (48.7-54.3)	57.3 (54.2-60.3)	67.1 (64-70.1)	71 (68.2-73.8)	**51.3 (50.3-52.3)**	
VTEC	Female	73	120	154	223	193	170	208	159	257	148	190	**1895**	0.412
	Male	64	71	83	131	134	107	118	112	152	115	135	**1222**	
	Ratio	0.9	0.6	0.5	0.6	0.7	0.6	0.6	0.7	0.6	0.8	0.7	**0.6**	
	Percentage (95% CI)	46.7 (38.1-55.4)	37.2 (30.3-44.4)	35.0 (29.0-41.5)	37.0 (32.0-42.3)	41.0 (35.6-46.5)	38.6 (32.9-44.6)	36.2 (31.0-41.7)	41.3 (35.4-47.4)	37.2 (32.5-42.0)	43.7 (37.6-50.0)	41.5 (36.1-47.1)	**39.2 (37.5-40.9)**	

[†]Chi-squared test for linear trend; CI, Confidence Interval; *Met threshold on rounding up.

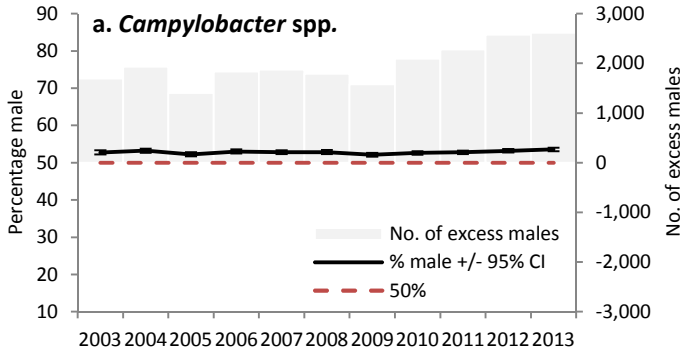
Ratios above a threshold of two or where the percentage male has a lower confidence interval above 50% are shaded.

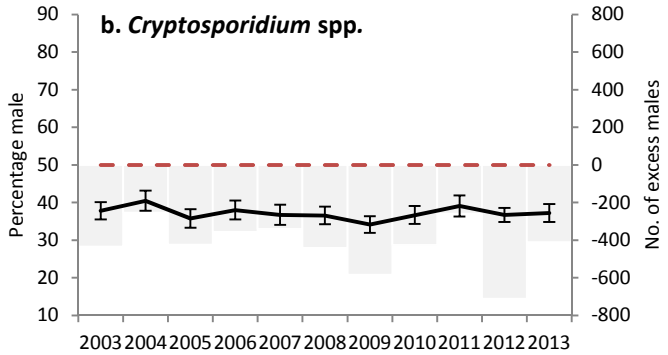
Table 4. Cases aged 16 to 65 years diagnosed with *Shigella flexneri* and *Shigella sonnei* infections with no reported travel history, by sex, male-to-female ratio and percentage male for selected serotypes, England, 2003–2013

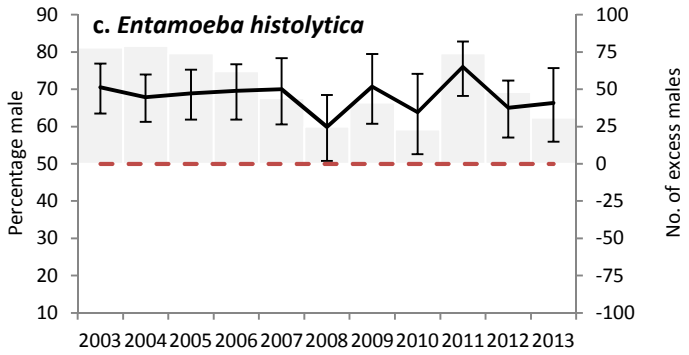
Organism	Serotype	Sex,m:f ratio and percentage male	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p value[†]
Shigella flexneri	All	Female	77	88	97	95	112	102	110	121	107	76	66	**1,051**	<0.001
		Male	65	73	92	95	101	121	137	204	208	257	349	**1,702**	
		Ratio	0.8	0.8	0.9	1.0	0.9	1.2	1.2	1.7	1.9	3.4	5.3	**1.6**	
		Percentage (95% CI)	45.8 (37.4-54.3)	45.3 (37.5-53.4)	48.7 (41.4-56.0)	50.0 (42.7-57.3)	47.4 (40.6-54.4)	54.3 (47.5-60.9)	55.5 (49.0-61.8)	62.8 (57.3-68.0)	66 (60.5-71.2)	77.2 (72.3-81.6)	84.1 (80.2-87.5)	**61.8 (60.0-63.6)**	
	PT 2a	Female	4	7	4	4	2	4	3	3	7	14	14	**66**	<0.001
		Male	3	2	5	4	0	4	7	6	21	42	74	**168**	
		Ratio	0.8	0.3	1.3	1.0	0.0	1.0	2.3	2.0	3.0	3.0	5.3	**2.5**	
		Percentage (95% CI)	42.9 (9.9-81.6)	22.2 (2.8-60.0)	55.6 (21.2-86.3)	50.0 (15.7-84.3)	0 (0-84.2)	50.0 (15.7-84.3)	70.0 (34.8-93.3)	66.7 (29.9-92.5)	75.0 (55.1-89.3)	75.0 (61.6-85.6)	84.1 (74.8-91)	**71.8 (65.6-77.5)**	
	PT 3a	Female	3	0	2	1	0	2	1	0	1	11	15	**36**	<0.001
		Male	2	1	1	0	7	4	4	8	23	82	170	**302**	
		Ratio	0.7	∞	0.5	0.0	∞	2.0	4.0	∞	23.0	7.5	11.3	**8.4**	
		Percentage (95% CI)	40.0 (5.3-85.3)	100 (2.5-100)	33.3 (0.8-90.6)	0 (0-97.5)	100 (59.0-100)	66.7 (22.3-95.7)	80 (28.4-99.5)	100 (63.1-100)	95.8 (78.9-99.9)	88.2 (79.8-93.9)	91.9 (87-95.4)	**89.3 (85.6-92.4)**	
Shigella sonnei	All	Female	212	253	326	271	387	304	414	409	261	184	195	**3,216**	<0.001
		Male	162	271	262	163	274	247	264	365	295	320	332	**2,955**	
		Ratio	0.8	1.1	0.8	0.6	0.7	0.8	0.6	0.9	1.1	1.7	1.7	**0.9**	
		Percentage (95% CI)	43.3 (38.2-48.5)	51.7 (47.3-56.1)	44.6 (40.5-48.7)	37.6 (33-42.3)	41.5 (37.7-45.3)	44.8 (40.6-49.1)	38.9 (35.2-42.7)	47.2 (43.6-50.7)	53.1 (48.8-57.3)	63.5 (59.1-67.7)	63 (58.7-67.1)	**47.9 (46.6-49.1)**	

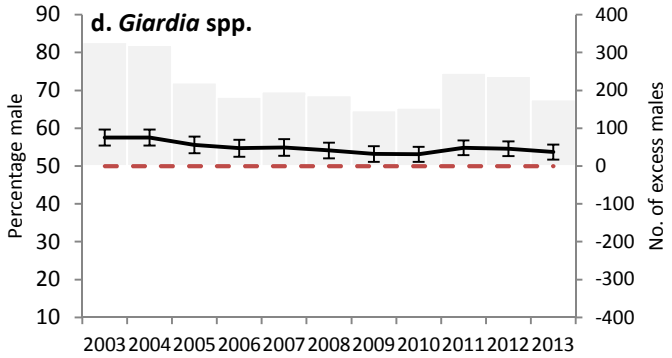
[†]Chi-squared test for linear trend; CI, Confidence Interval.

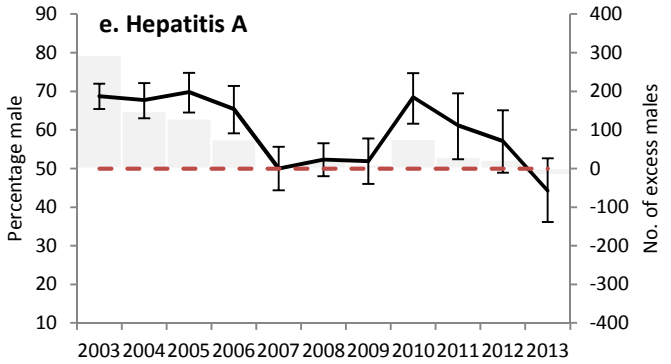
Ratios above a threshold of two or where the percentage male has a lower confidence interval above 50% are shaded.

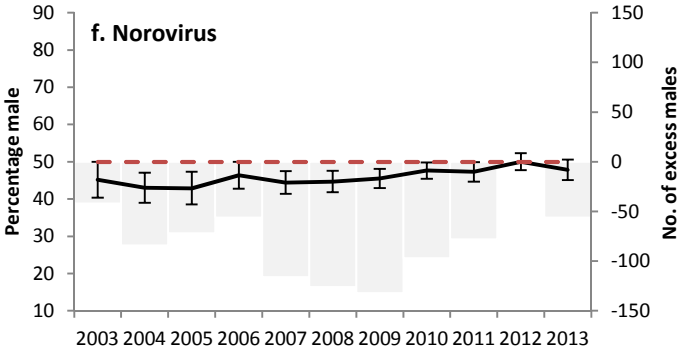

a. Campylobacter spp.
Percentage male
No. of excess males
No. of excess males
% male +/- 95% CI
50%
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

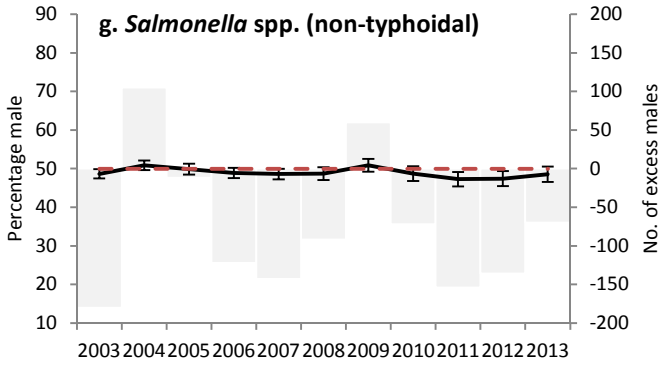

b. Cryptosporidium spp.
Percentage male
No. of excess males
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

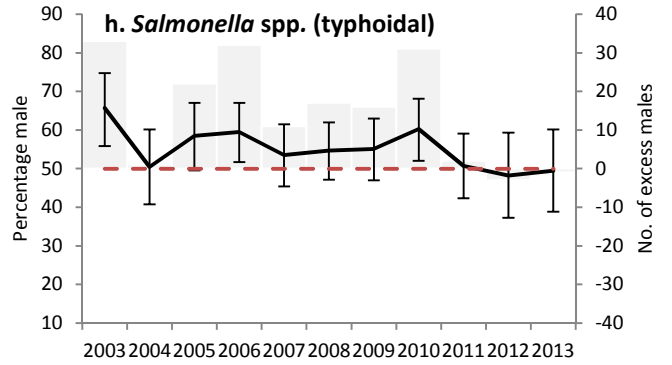

c. Entamoeba histolytica
Percentage male
No. of excess males
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

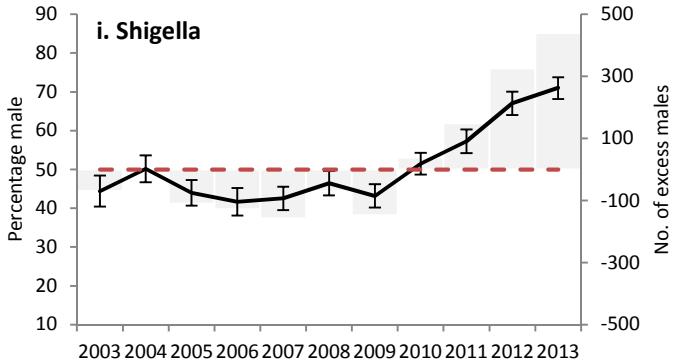

d. Giardia spp.
Percentage male
No. of excess males
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

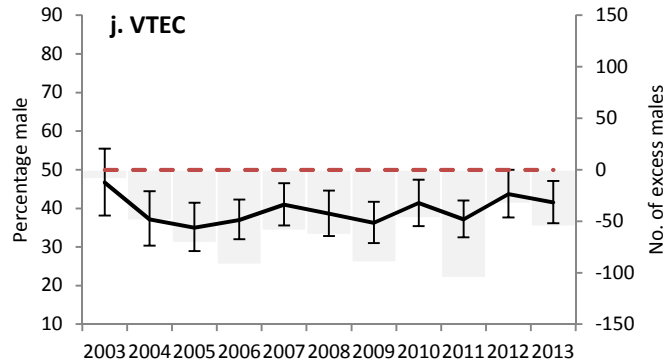

e. Hepatitis A
Percentage male
No. of excess males
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

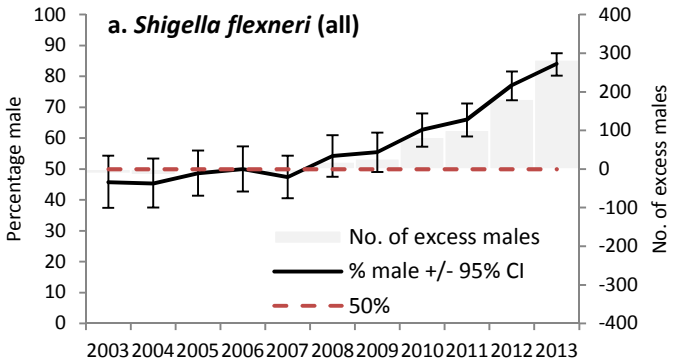

f. Norovirus
Percentage male
No. of excess males
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

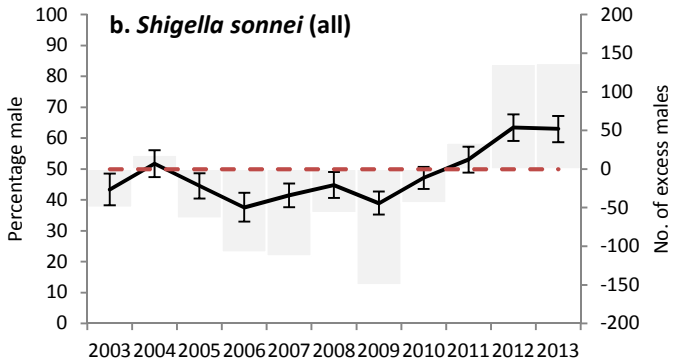

g. Salmonella spp. (non-typhoidal)
Percentage male
No. of excess males
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

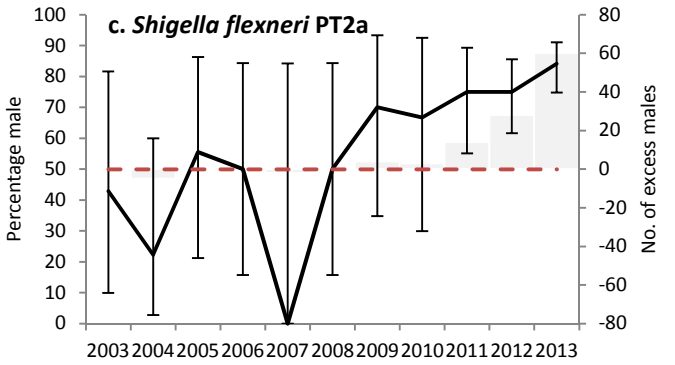

h. Salmonella spp. (typhoidal)
Percentage male
No. of excess males
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

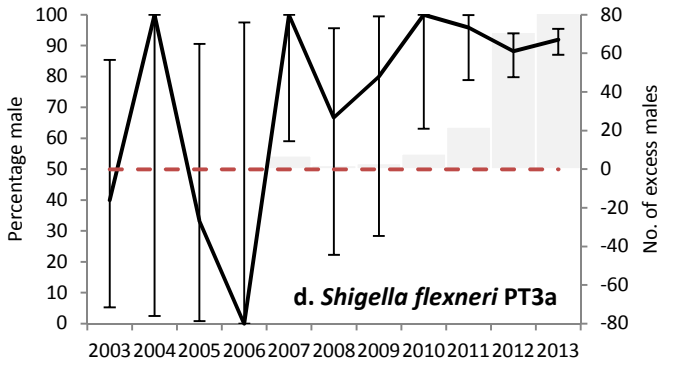

i. Shigella
Percentage male
No. of excess males
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013


j. VTEC
Percentage male
No. of excess males
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013


a. Shigella flexneri (all)
Percentage male
No. of excess males
No. of excess males
% male +/- 95% CI
50%
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013


b. Shigella sonnei (all)
Percentage male
No. of excess males
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013


c. Shigella flexneri PT2a
Percentage male
No. of excess males
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013


d. Shigella flexneri PT3a
Percentage male
No. of excess males
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

Epidemiology and Infection: Use of gender distribution in routine surveillance data to detect potential transmission of gastrointestinal infections among men who have sex with men in England

P Mook, D Gardiner, S Kanagarajah, M Kerac, G Hughes, N Field, N McCarthy, C Rawlings, I Simms, C Lane, P. D. Crook

Supplementary material

S 1. Cases aged 16 to 65 years diagnosed with *Shigella* spp. infection with no reported travel history, by sex, male-to-female ratio and percentage male for age groups and high and low-risk locations, England, 2003–2013

Age group or location	Sex, m:f ratio & percent-age male	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p value†
<16 years	Female	107	114	124	105	123	133	122	145	132	125	99	**1329**	0.388
	Male	99	134	125	120	124	150	130	159	158	130	118	**1447**	
	Ratio	0.9	1.2	1.0	1.1	1.0	1.1	1.1	1.1	1.2	1.0	1.2	**1.1**	
	Percentage (95% CI)	48.1 (41.1-55.1)	54 (47.6-60.4)	50.2 (43.8-56.6)	53.3 (46.6-60.0)	50.2 (43.8-56.6)	53.0 (47.0-58.9)	51.6 (45.2-57.9)	52.3 (46.5-58)	54.5 (48.6-60.3)	51.0 (44.7-57.3)	54.4 (47.5-61.1)	**52.1 (50.2-54)**	
16-24 years	Female	50	90	88	78	108	80	137	117	74	42	53	**917**	<0.001
	Male	44	43	52	29	71	71	54	63	63	69	76	**635.0**	
	Ratio	0.9	0.5	0.6	0.4	0.7	0.9	0.4	0.5	0.9	1.6	1.4	**0.7**	
	Percentage (95% CI)	46.8 (36.4-57.4)	32.3 (24.5-41)	37.1 (29.1-45.7)	27.1 (19.0-36.6)	39.7 (32.4-47.2)	47.0 (38.9-55.3)	28.3 (22.0-35.2)	35.0 (28.1-42.4)	46.0 (37.4-54.7)	62.2 (52.5-71.2)	58.9 (49.9-67.5)	**40.9 (38.5-43.4)**	
25-49 years	Female	224	236	310	278	366	317	349	335	256	199	186	**3056**	<0.001
	Male	186	265	269	208	280	270	324	454	393	475	541	**3665**	
	Ratio	0.8	1.1	0.9	0.7	0.8	0.9	0.9	1.4	1.5	2.4	2.9	**1.2**	
	Percentage (95% CI)	45.4 (40.5-50.3)	52.9 (48.4-57.3)	46.5 (42.3-50.6)	42.8 (38.4-47.3)	43.3 (39.5-47.3)	46.0 (41.9-50.1)	48.1 (44.3-52.0)	57.5 (54.0-61.0)	60.6 (56.7-64.3)	70.5 (66.9-73.9)	74.4 (71.1-77.6)	**54.5 (53.3-55.7)**	
50-65 years	Female	68	84	112	91	134	130	126	159	104	73	63	**1144**	<0.001
	Male	43	105	79	82	99	116	87	132	126	96	124	**1089**	
	Ratio	0.6	1.3	0.7	0.9	0.7	0.9	0.7	0.8	1.2	1.3	2.0*	**1.0**	
	Percentage (95% CI)	38.7 (29.6-48.5)	55.6 (48.2-62.8)	41.4 (34.3-48.7)	47.4 (39.8-55.1)	42.5 (36.1-49.1)	47.2 (40.8-53.6)	40.8 (34.2-47.8)	45.4 (39.5-51.3)	54.8 (48.1-61.3)	56.8 (49.0-64.4)	66.3 (59.1-73.0)	**48.8 (46.7-50.9)**	
Brighton, London or Manchester	Female	92	116	136	112	147	147	166	136	149	124	117	**1442**	<0.001
	Male	107	174	125	111	155	161	194	277	270	359	470	**2403**	
	Ratio	1.2	1.5	0.9	1.0	1.1	1.1	1.2	2.0	1.8	2.9	4.0	**1.7**	
	Percentage (95% CI)	53.8 (46.6-60.8)	60 (54.1-65.7)	47.9 (41.7-54.1)	49.8 (43.0-56.5)	51.3 (45.5-57.1)	52.3 (46.5-58.0)	53.9 (48.6-59.1)	67.1 (62.3-71.6)	64.4 (59.6-69.0)	74.3 (70.2-78.2)	80.1 (76.6-83.2)	**62.5 (60.9-64)**	
Other location	Female	250	294	374	335	461	380	446	475	285	190	185	**3675**	<0.001
	Male	166	239	275	208	295	296	271	372	312	281	271	**2986**	
	Ratio	0.7	0.8	0.7	0.6	0.6	0.8	0.6	0.8	1.1	1.5	1.5	**0.8**	
	Percentage (95% CI)	39.9 (35.2-44.8)	44.8 (40.6-49.2)	42.4 (38.5-46.3)	38.3 (34.2-42.5)	39.0 (35.5-42.6)	43.8 (40.0-47.6)	37.8 (34.2-41.5)	43.9 (40.5-47.3)	52.3 (48.2-56.3)	59.7 (55.1-64.1)	59.4 (54.8-64.0)	**44.8 (43.6-46)**	

†Chi-squared test for linear trend; CI, Confidence Interval; *Met threshold on rounding up.

Ratios above a threshold of two or where the percentage male has a lower confidence interval above 50% are shaded.

S 2. Cases aged 16 to 65 years diagnosed with *Entamoeba histolytica* infection with no reported travel history, by sex, male-to-female ratio and percentage male for age groups and high and low-risk locations, England, 2003–2013

Age group or location	Sex, m:f ratio & percentage male	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p value†
<16 years	Female	9	3	2	3	6	2	4	3	4	7	4	**47**	0.325
	Male	6	3	5	5	4	12	5	7	9	8	2	**66**	
	Ratio	0.7	1.0	2.5	1.7	0.7	6.0	1.3	2.3	2.3	1.1	0.5	**1.4**	
	Percentage (95% CI)	40.0 (16.3-67.7)	50.0 (11.8-88.2)	71.4 (29.0-96.3)	62.5 (24.5-91.5)	40.0 (12.2-73.8)	85.7 (57.2-98.2)	55.6 (21.2-86.3)	70.0 (34.8-93.3)	69.2 (38.6-90.9)	53.3 (26.6-78.7)	33.3 (4.3-77.7)	**58.4 (48.8-67.6)**	
16-24 years	Female	13	13	11	4	5	9	3	8	6	11	3	**86**	0.86
	Male	12	12	13	8	6	7	7	6	10	14	7	**102.0**	
	Ratio	0.9	0.9	1.2	2.0	1.2	0.8	2.3	0.8	1.7	1.3	2.3	**1.2**	
	Percentage (95% CI)	48.0 (27.8-68.7)	48.0 (27.8-68.7)	54.2 (32.8-74.4)	66.7 (34.9-90.1)	54.5 (23.4-83.3)	43.8 (19.8-70.1)	70.0 (34.8-93.3)	42.9 (17.7-71.1)	62.5 (35.4-84.8)	56.0 (34.9-75.6)	70.0 (34.8-93.3)	**54.3 (46.8-61.5)**	
25-49 years	Female	35	44	38	30	18	38	20	19	21	35	20	**318**	0.313
	Male	102	114	93	87	55	57	49	37	68	70	37	**769**	
	Ratio	2.9	2.6	2.4	2.9	3.1	1.5	2.5	1.9	3.2	2.0	1.9	**2.4**	
	Percentage (95% CI)	74.5 (66.3-81.5)	72.2 (64.5-79)	71.0 (62.4-78.6)	74.4 (65.5-82)	75.3 (63.9-84.7)	60.0 (49.4-69.9)	71.0 (58.8-81.3)	66.1 (52.2-78.2)	76.4 (66.2-84.8)	66.7 (56.8-75.6)	64.9 (51.1-77.1)	**70.7 (67.9-73.4)**	
50-65 years	Female	8	14	12	14	10	4	6	3	7	10	9	**97**	0.574
	Male	20	24	29	15	16	12	14	10	30	20	19	**209**	
	Ratio	2.5	1.7	2.4	1.1	1.6	3.0	2.3	3.3	4.3	2.0	2.1	**2.2**	
	Percentage (95% CI)	71.4 (51.3-86.8)	63.2 (46.0-78.2)	70.7 (54.5-83.9)	51.7 (32.5-70.6)	61.5 (40.6-79.8)	75.0 (47.6-92.7)	70.0 (45.7-88.1)	76.9 (46.2-95)	81.1 (64.8-92)	66.7 (47.2-82.7)	67.9 (47.6-84.1)	**68.3 (62.8-73.5)**	
Brighton. London or Manchester	Female	27	30	40	10	4	8	7	12	12	19	10	**179**	0.132
	Male	76	88	88	70	22	24	25	20	41	43	22	**519**	
	Ratio	2.8	2.9	2.2	7.0	5.5	3.0	3.6	1.7	3.4	2.3	2.2	**2.9**	
	Percentage (95% CI)	73.8 (64.2-82.0)	74.6 (65.7-82.1)	68.8 (60.0-76.6)	87.5 (78.2-93.8)	84.6 (65.1-95.6)	75.0 (56.6-88.5)	78.1 (60.0-90.7)	62.5 (43.7-78.9)	77.4 (63.8-87.7)	69.4 (56.3-80.4)	68.8 (50.0-83.9)	**74.4 (70.9-77.6)**	
Other location	Female	29	41	21	38	29	43	22	18	22	37	22	**322**	0.100
	Male	58	62	47	40	55	52	45	33	67	61	41	**561**	
	Ratio	2.0	1.5	2.2	1.1	1.9	1.2	2.0	1.8	3.0	1.6	1.9	**1.7**	
	Percentage (95% CI)	66.7 (55.7-76.4)	60.2 (50.1-69.7)	69.1 (56.7-79.8)	51.3 (39.7-62.8)	65.5 (54.3-75.5)	54.7 (44.2-65.0)	67.2 (54.6-78.2)	64.7 (50.1-77.6)	75.3 (65.0-83.8)	62.2 (51.9-71.8)	65.1 (52.0-76.7)	**63.5 (60.3-66.7)**	

†Chi-squared test for linear trend; CI, Confidence Interval.Ratios above a threshold of two or where the percentage male has a lower confidence interval above 50% are shaded.

S3. Cases aged 16 to 65 years diagnosed with Hepatitis A infection with no reported travel history, by sex, male-to-female ratio and percentage male for age groups and high and low-risk locations, England, 2003–2013

Age group or location	Sex, m:f ratio & percentage male	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p value†
<16 years	Female	82	49	28	50	26	37	19	33	26	28	33	**411**	0.635
	Male	79	53	37	39	27	36	40	44	30	31	25	**441**	
	Ratio	1.0	1.1	1.3	0.8	1.0	1.0	2.1	1.3	1.2	1.1	0.8	**1.1**	
	Percentage (95% CI)	49.1 (41.1-57.1)	52.0 (41.8-62.0)	56.9 (44.0-69.2)	43.8 (33.3-54.7)	50.9 (36.8-64.9)	49.3 (37.4-61.3)	67.8 (54.4-79.4)	57.1 (45.4-68.4)	53.6 (39.7-67.0)	52.5 (39.1-65.7)	43.1 (30.2-56.8)	**51.8 (48.3-55.2)**	
16-24 years	Female	93	37	22	21	26	49	31	21	12	12	22	**346**	<0.001
	Male	205	52	43	46	27	52	38	33	17	25	11	**549.0**	
	Ratio	2.2	1.4	2.0*	2.2	1.0	1.1	1.2	1.6	1.4	2.1	0.5	**1.6**	
	Percentage (95% CI)	68.8 (63.2-74.0)	58.4 (47.5-68.8)	66.2 (53.4-77.4)	68.7 (56.2-79.4)	50.9 (36.8-64.9)	51.5 (41.3-61.6)	55.1 (42.6-67.1)	61.1 (46.9-74.1)	58.6 (38.9-76.5)	67.6 (50.2-82.0)	33.3 (18.0-51.8)	**61.3 (58.1-64.5)**	
25-49 years	Female	119	67	45	40	98	165	73	27	27	37	40	**738**	<0.001
	Male	289	188	141	79	105	182	83	80	46	43	42	**1278**	
	Ratio	2.4	2.8	3.1	2.0*	1.1	1.1	1.1	3.0	1.7	1.2	1.1	**1.7**	
	Percentage (95% CI)	70.8 (66.2-75.2)	73.7 (67.9-79.0)	75.8 (69-81.8)	66.4 (57.2-74.8)	51.7 (44.6-58.8)	52.4 (47.0-57.8)	53.2 (45.1-61.2)	74.8 (65.4-82.7)	63.0 (50.9-74.0)	53.8 (42.2-65.0)	51.2 (39.9-62.4)	**63.4 (61.2-65.5)**	
50-65 years	Female	32	31	31	23	35	46	36	17	13	17	21	**302**	0.143
	Male	43	43	43	34	27	51	30	28	19	20	13	**351**	
	Ratio	1.3	1.4	1.4	1.5	0.8	1.1	0.8	1.6	1.5	1.2	0.6	**1.2**	
	Percentage (95% CI)	57.3 (45.4-68.7)	58.1 (46.1-69.5)	58.1 (46.1-69.5)	59.6 (45.8-72.4)	43.5 (31.0-56.7)	52.6 (42.2-62.8)	45.5 (33.1-58.2)	62.2 (46.5-76.2)	59.4 (40.6-76.3)	54.1 (36.9-70.5)	38.2 (22.2-56.4)	**53.8 (49.8-57.6)**	
Brighton. London or Manchester	Female	18	18	14	14	68	197	59	12	21	21	36	**478**	0.001
	Male	49	37	38	25	52	191	53	36	27	24	30	**562**	
	Ratio	2.7	2.1	2.7	1.8	0.8	1.0	0.9	3.0	1.3	1.1	0.8	**1.2**	
	Percentage (95% CI)	73.1 (60.9-83.2)	67.3 (53.3-79.3)	73.1 (59-84.4)	64.1 (47.2-78.8)	43.3 (34.3-52.7)	49.2 (44.1-54.3)	47.3 (37.8-57.0)	75.0 (60.4-86.4)	56.3 (41.2-70.5)	53.3 (37.9-68.3)	45.5 (33.1-58.2)	**54.0 (51.0-57.1)**	
Other location	Female	226	117	84	70	91	63	81	53	31	45	47	**908**	<0.001
	Male	488	246	189	134	107	94	98	105	55	64	36	**1616**	
	Ratio	2.2	2.1	2.3	1.9	1.2	1.5	1.2	2.0*	1.8	1.4	0.8	**1.8**	
	Percentage (95% CI)	68.3 (64.8-71.7)	67.8 (62.7-72.6)	69.2 (63.4-74.7)	65.7 (58.7-72.2)	54.0 (46.8-61.1)	59.9 (51.8-67.6)	54.7 (47.2-62.2)	66.5 (58.5-73.8)	64.0 (52.9-74.0)	58.7 (48.9-68.1)	43.4 (32.5-54.7)	**64.0 (62.1-65.9)**	

†Chi-squared test for linear trend; CI, Confidence Interval; *Met threshold on rounding up.
Ratios above a threshold of two or where the percentage male has a lower confidence interval above 50% are shaded.

S 4. Cases aged 16 to 65 years diagnosed with typhoidal *Salmonella* spp. infection with no reported travel history, by sex, male-to-female ratio and percentage male for age groups and high and low-risk locations, England, 2003–2013

Age group or location	Sex, m:f ratio & percentage male	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p value†
<16 years	Female	19	14	16	21	21	20	43	21	22	11	4	**212**	0.373
	Male	23	21	24	19	42	22	22	31	18	13	10	**245**	
	Ratio	1.2	1.5	1.5	0.9	2.0	1.1	0.5	1.5	0.8	1.2	2.5	**1.2**	
	Percentage (95% CI)	54.8 (38.7-70.2)	60 (42.1-76.1)	60 (43.3-75.1)	47.5 (31.5-63.9)	66.7 (53.7-78.0)	52.4 (36.4-68.0)	33.8 (22.6-46.6)	59.6 (45.1-73.0)	45 (29.3-61.5)	54.2 (32.8-74.4)	71.4 (41.9-91.6)	**53.6 (48.9-58.3)**	
16-24 years	Female	11	13	12	13	17	21	19	20	17	11	13	**167**	0.073
	Male	23	12	17	20	26	25	24	29	20	7	8	**211**	
	Ratio	2.1	0.9	1.4	1.5	1.5	1.2	1.3	1.5	1.2	0.6	0.6	**1.3**	
	Percentage (95% CI)	67.6 (49.5-82.6)	48 (27.8-68.7)	58.6 (38.9-76.5)	60.6 (42.1-77.1)	60.5 (44.4-75.0)	54.3 (39.0-69.1)	55.8 (39.9-70.9)	59.2 (44.2-73.0)	54.1 (36.9-70.5)	38.9 (17.3-64.3)	38.1 (18.1-61.6)	**55.8 (50.7-60.9)**	
25-49 years	Female	21	30	37	43	45	50	39	33	43	24	25	**390**	0.463
	Male	38	34	51	72	46	65	54	55	47	30	31	**523**	
	Ratio	1.8	1.1	1.4	1.7	1	1.3	1.4	1.7	1.1	1.3	1.2	**1.3**	
	Percentage (95% CI)	64.4 (50.9-76.4)	53.1 (40.2-65.7)	58.0 (47.0-68.4)	62.6 (53.1-71.5)	50.5 (39.9-61.2)	56.5 (47.0-65.7)	58.1 (47.4-68.2)	62.5 (51.5-72.6)	52.2 (41.4-62.9)	55.6 (41.4-69.1)	55.4 (41.5-68.7)	**57.3 (54.0-60.5)**	
50-65 years	Female	4	11	5	12	11	12	13	7	12	9	8	**104**	0.114
	Male	8	9	8	8	12	10	9	7	7	4	6	**88**	
	Ratio	2	0.8	1.6	0.7	1.1	0.8	0.7	1	0.6	0.4	0.8	**0.8**	
	Percentage (95% CI)	66.7 (34.9-90.1)	45.0 (23.1-68.5)	61.5 (31.6-86.1)	40.0 (19.1-63.9)	52.2 (30.6-73.2)	45.5 (24.4-67.8)	40.9 (20.7-63.6)	50.0 (23.0-77.0)	36.8 (16.3-61.6)	30.8 (9.1-61.4)	42.9 (17.7-71.1)	**45.8 (38.6-53.2)**	
Brighton. London or Manchester	Female	20	31	19	39	40	44	31	34	38	26	21	**343**	0.199
	Male	41	31	39	45	41	62	36	58	47	19	24	**443**	
	Ratio	2.1	1	2.1	1.2	1	1.4	1.2	1.7	1.2	0.7	1.1	**1.3**	
	Percentage (95% CI)	67.2 (54.0-78.7)	50.0 (37.0-63.0)	67.2 (53.7-79.0)	53.6 (42.4-64.5)	50.6 (39.3-61.9)	58.5 (48.5-68.0)	53.7 (41.1-66.0)	63.0 (52.3-72.9)	55.3 (44.1-66.1)	42.2 (27.7-57.8)	53.3 (37.9-68.3)	**56.4 (52.8-59.9)**	
Other location	Female	16	23	35	29	33	39	40	26	34	18	25	**318**	0.094
	Male	28	24	37	55	43	38	51	33	27	22	21	**379**	
	Ratio	1.8	1	1.1	1.9	1.3	1	1.3	1.3	0.8	1.2	0.8	**1.2**	
	Percentage (95% CI)	63.6 (47.8-77.6)	51.1 (36.1-65.9)	51.4 (39.3-63.3)	65.5 (54.3-75.5)	56.6 (44.7-67.9)	49.4 (37.8-61.0)	56.0 (45.2-66.4)	55.9 (42.4-68.8)	44.3 (31.5-57.6)	55.0 (38.5-70.7)	45.7 (30.9-61.0)	**54.4 (50.6-58.1)**	

†Chi-squared test for linear trend; CI, Confidence Interval.
Ratios above a threshold of two or where the percentage male has a lower confidence interval above 50% are shaded.